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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/635,864	08/10/2000	Jeffrey M. Friedman	600-1-087CIP1	6312

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No.	Applicant(s)	
	09/635,864	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-67 and 69-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-67 and 69-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 61-67, 69-75, 77-79, 82-84, and 87-88 have been amended and claims 89-102 have been added in the amendment filed 12 February 2007. Claims 1-60 and 68 have been canceled. Claims 61-67 and 69-102 are pending and under examination in the instant Office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 12 February 2007 have been fully considered but they are not deemed to be persuasive.

Information Disclosure Statement

The information disclosure statement filed 22 May 2006 was considered in its entirety and the initialed and signed copies were sent with the previous Office action (as evidenced by Doc Code 1449 dated 08/08/2006).

Applicant should note that there appears to be a typographical error in the spelling of the inventor's name. The name currently appears as "Friedman" in the instant application, but is "Freidman" on the IDS.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 63 (and dependent claims 69-88 and 93-102) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record in the previous Office action.

Applicant argues at page 13 of the response that the specification provides an alignment of the human and mouse protein in Figure 4 and demonstrates that 83% of the amino acids are identical between the two proteins. Applicant argues that these molecules are exemplary and the specification discloses that "interspecies OB polypeptides homology is high, and as much as greater than 80% homologous". This argument has been considered, but is not persuasive. At page 5 of the specification it is stated that "ob polypeptides from various species **may** be highly homologous" (emphasis added). The next part of the sentence states "murine and human ob polypeptides are greater than 80% homologous". Therefore, the specification fails to state that interspecies OB polypeptides are as much as greater than 80% homologous, as asserted by Applicant.

Applicant compares the similarities between murine and human OB polypeptides and encoding nucleic acids at pages 13 and 14 of the response. Applicant argues that "there is little substantial degree of variation between species within the claimed genus". Applicant's argument has been fully considered, but is not persuasive. The specification discloses two species of OB protein which are 83% identical to one another. However, the claims are directed to OB proteins which are 83% identical to either the murine or the human OB protein – this equates to hypothetical proteins which differ from one another by as much as 34% between different molecules. The single disclosure of 83% is not a basis for the broad claim of the range 83% or greater amino acid sequence identity in the instant specification as originally filed.

Applicant argues at page 14 of the response that the instant specification describes a representative number of examples, such that the skilled artisan would recognize that Applicant was in possession of the claimed invention. Applicant's argument has been fully considered, but is not persuasive. Applicant's two species do not even encompass the complete range of molecules which are being claimed (i.e. 83% identity to the murine can equate to as much as 34% variation from the human and vice versa). Therefore, the disclosure of the murine and human species of OB protein do not appear to be representative of the entire genus of molecules which are 83% identical to either the murine or the human OB proteins, absent evidence to the contrary.

Applicant argues at page 15 of the response that "a substantial portion of each of the interspecies sequence is, in fact, explicitly disclosed by virtue of the hybridization

conditions employed in the assays which afforded their isolation, which required high homology to the G27 probe, which contains almost an entire exon of the mouse OB coding sequence". Applicant's argument has been considered, but is not found persuasive. First, Applicant is arguing limitations not present in the claims, as the claims do not require the G27 probe. Secondly, the fact that a nucleic acid may hybridize to a given sequence does not provide for a molecule which encodes a protein with any particular function. Applicant has not equated nucleic acid hybridization with encoding a protein with a particular function. Furthermore, a method of isolating a molecule is not a written description of the molecule.

Applicant asserts that the presence of a number of "homologous" sequences were identified using hybridization techniques. However, there is no disclosure as to the structure of these nucleic acids or the encoded proteins, so there is no disclosure that any of the encoded proteins were at least 83% identical. Applicant refers to Exhibits 1-7 which provide amino acid sequence alignments for various OB proteins with the human and mouse proteins. However, Applicant was not in possession of these molecules at the time of the instant invention. Applicant did not have possession of the nucleic acids encoding these proteins. The fact that Figure 16 of the instant specification shows hybridization of a probe to nucleic acid from various species is interesting, but it does not describe those molecules which stuck to the probe. Nor does it demonstrate that the nucleic acid molecules which stuck to the probe encoded a protein with any particular function. Therefore, it does not support a written description for the claimed genus (see *Vas-Cath In. v. Mahurkar*, 19 USPQ2d 1111).

Claim 77 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ***isolated or cultured*** cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record in the previous Office action.

Applicant argues that the application teaches a number of suitable cell and tissue types from which host cells may be selected for transformation, including mammalian host cells and human cells in tissue culture. Applicant asserts that the claims have no recitation concerning efficacy of transgene expression in transgenic animals. Applicant argues that they are entitled to claims that are commensurate in scope with what they have exemplified and which which one of skill in the art could obtain by virtue of that which the applicant has disclosed and asserts that the claims are enabled.

Applicant's arguments have been fully considered, but are not persuasive. In so far as the claim reads on a host cell in the context of a multicellular, transgenic organism and a host cell intended for gene therapy, the specification is not enabled. There are no methods or working examples disclosed in the instant application whereby cells were transplanted in a subject and the cells were demonstrated to express the OB polypeptide or where gene therapy was performed on a human. The unpredictability of

the art is *very high* with regards to making transgenic animals as pointed out in the previous Office action. Applicant has offered no evidence to the contrary.

With regard to transplantation of cells expressing the OB polypeptide, the specification does not teach any methods or working examples that indicate a OB nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Therefore, undue experimentation would be required of the skilled artisan to introduce and express an OB nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express an OB nucleic acid in the cell of an organism or be able to produce an OB protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the OB protein and to introduce and express an OB nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce an OB nucleic acid in the cell of an organism to be able produce that OB polypeptide, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (As indicated in the previous Office

action, this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Claims 61-62 (and dependent claims 69-102) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 61 and 62 recite "wherein said OB polypeptide comprises an amino acid sequence set out in". The recitation of "an amino acid sequence" encompasses any and all sequences which could be made from the reference sequence of SEQ ID NO:2, 4, 5 or 6 - this includes fragments and non-contiguous sequences of the reference sequence. The instant specification fails to describe all fragments and sequences which can be made from SEQ ID NO:2, 4, 5 or 6. The instant specification fails to describe any polypeptides other than the polypeptides of SEQ ID NO:2, 4, 5 and 6. First, the instant specification teaches a murine and human protein, and fails to teach any other polypeptides or any variation from the disclosed amino acid sequences. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of proteins of SEQ ID NO:2, 4, 5 and 6. The subject matter that is claimed is described above. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to

a predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are not limited to any particular polypeptide, in that the claims are directed to variant forms (based on the recitation of "an amino acid sequence". The specification only describes polypeptides having the amino acid sequence of SEQ ID NO:2, 4, 5 and 6 and fails to teach or describe any other molecules which meet the structural limitations of the claims. The breadth of the claims is such that the claims encompass polypeptides from other species, related polypeptides and variants which have yet to be described. There is a lack of guidance or teaching regarding structure and function of the polypeptide because there is only the example of murine and human polypeptides provided in the specification and because there is no guidance found in the prior art for these specific polypeptides.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims except for the polypeptides of SEQ ID NO:2, 4, 5 and 6. The specification does not provide a complete structure of those molecules which have **an** amino acid sequence of SEQ ID NO:2, 4, 5 and 6 and retain the function required by the claims. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation

between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus because the specification teaches the murine and human proteins, but no variants as are encompassed by the claims. Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 61-67, 69-88 and newly added claims 89-102 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,935,810 and claims 1-21 of U.S. Patent No. 6,309,853 for the reasons of record in the previous Office actions and further in view of Davis et al. (U.S. Pat. No. 4,179,337) and Stahl et al. (U.S. Pat. No. 5,470,843).

Applicant argues that none of the secondary references, singly or when combined, teach or suggest a modification of the claimed molecules of the '810 or '853 reference such that the OB-fusion protein encoding molecules encompassed by the instant claims would result. Applicant's argument has been considered, but is not persuasive. As pointed out previously, polypeptides having one or more polymers attached to the polypeptides is old and well known in the art. Davis et al. teach that coupling of biologically active polypeptides to polymers is beneficial to increase the stability and circulation time of the polypeptide as well as decreasing immunogenicity (see columns 1-2). Therefore, there is motivation in the art for adding a polymer to a polypeptide of interest to increase stability and circulation time. Secondly, Stahl et al. was cited as teaching polymers which are suitable for *in vivo* use, including polyaminoacids (see column 7, lines 4-13). One would be motivated to use a polymer which is suitable for *in vivo* use, and polyaminoacids meet this requirement. Therefore, it would have been *prima facie* obvious to attach a polymer, specifically a polyaminoacid, to the leptin (OB) molecule of the '810 or '853 patent for the advantage of increased stability and circulation time as well as for decreased immunogenicity. Additionally, because polyaminoacids can be encoded by a nucleic acid, it also would

have been *prima facie* obvious to make such molecules using a nucleic acid that encoded a fusion protein of leptin (OB) and the polyaminoacid polymer because this would eliminate the additional step of coupling the polyaminoacid polymer to the protein of interest. One would have a reasonable expectation of success in generating such a molecule because generation of fusion proteins was routine in the art at the time of the instant invention, as was use of polymers with biologically active proteins as evidenced by Davis et al. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

With regard to Applicant's request to defer the rejection, there are no provisions for such and the rejection is being maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud